Letter to the Editor

Falciparum malaria and Tangier disease

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A 29-year-old German man of Caucasian origin presented with a 3-day history of headache, malaise and fever following a 4-week trip to The Gambia, West Africa. He did not receive any pre-travel vaccinations, and nor did he take malaria prophylaxis, but he remained well throughout his journey and for 1 week afterwards, until he fell acutely ill. Except for a moderately enlarged spleen (18 cm in diameter), his physical examination was unremarkable. A chest radiograph and an electrocardiogram were normal. Laboratory tests on admission were normal except for moderate thrombocytopenia (75/nL) and low haptoglobin (28 mg/dL). Lactate dehydrogenase (LDH) (357 U/L), total bilirubin (1.1 mg/dL) and C-reactive protein (5.2 mg/dL) levels were slightly elevated. As suspected, microscopy of Giemsa-stained thick and thin blood films showed *Plasmodium falciparum* trophozoites at moderate density, with approximately 2% of erythrocytes infected. A lipid profile performed on a fasting blood sample during his stay in hospital revealed low total cholesterol (27 mg/dL) with a very low level of HDL-cholesterol (3 mg/dL), apolipoprotein A1 below detection levels, and a raised triglyceride level (231 mg/dL), a characteristic pattern which has been observed in malaria patients before.[1–3] Our patient received 10 mg/kg per day quinine three times daily orally and was clinically and parasitologically cured on day 7, with no signs of recrudescence on day 28. Whereas hemolysis parameters returned to normal, splenomegaly, thrombocytopenia and the abnormal plasma lipid pattern persisted at about the same level. When giving his medical history, our patient had stated that he underwent tonsillectomy early in childhood in connection with a rare disease that previously attending physicians had suggested before. This led us to suspect Tangier disease. The diagnosis was confirmed by demonstration by Schmitz and co-workers[4] of two novel mutations, denoted C2665del and C4457T, of the ABCA1 gene, coding for the ATP-binding cassette transporter 1. Its dysfunction due to various mutations had been recently identified as the cause of not only Tangier disease[5–7] but also another familial high-density lipoprotein (HDL) deficiency[8] syndrome, a more frequently occurring, related condition in which HDL deficiency is less pronounced.

Tangier disease is a rare autosomal recessive disorder of lipid metabolism. Failure to convert cholesterol to HDL and to expel it from the cell leads to low levels of serum cholesterol and very low HDL and apolipoprotein A levels. Owing to storage of cholesterol esters in the reticuloendothelial system (RES), hypertrophy and orange–yellow discoloration of the pharyngeal tonsils and mild to moderate (hepato) splenomegaly are common, as is thrombocytopenia. Premature coronary artery disease (CAD) and a syringomyelia-like neurologic syndrome may occur.[9] To our knowledge, about 60 cases of Tangier disease have been described so far worldwide. This is the first report on falciparum malaria coinciding with Tangier disease. In both conditions, different pathomechanisms lead to thrombocytopenia, splenomegaly (often combined with moderate hepatomegaly), and strikingly similar plasma lipid changes. In both diseases, thrombocyte function is not impaired. In Tangier disease, these features are explained by lipid infiltration of bone marrow and RES, with hypersplenism possibly contributing to a minor extent. Plasma lipid changes represent the primary problem leading to secondary organ alterations and long-term sequelae. In malaria, the spleen plays an essential role in limiting the acute expansion of the infection by removing parasitized erythrocytes, and thrombocytopenia is mainly due to hypersplenism. In non-immune patients, hepatosplenomegaly and thrombocytopenia are reversible after treatment of malaria, and plasma lipid alterations are transient and limited to the parasitemic phase. Temporary HDL depletion has been observed in over 90% in some studies. A decrease in HDL-C levels as part of the acute-phase reaction, diminished hepatic synthesis due to affliction of the liver, and direct and parasite–lipoprotein interactions, have been suggested as possible reasons. Although there is little immediate clinical relevance of this phenomenon, it has been suggested as an adjuvant diagnostic tool by some authors.[1–3] Co-morbidity did not influence the course of disease in our patient, but clinical aggravation of malaria appears to be possible in Tangier disease patients, particularly if the immediate diagnosis of falciparum malaria is delayed for some reason. In any case, regression of spleen

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size and normalization of platelet count and plasma lipid pattern cannot be used as secondary markers for recovery from malaria once co-morbidity with Tangier disease exists.

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